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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,951	02/28/2005	Doron Shabat	29195	2616

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MARTIN D. MOYNIHAN d/b/a PRTSI, INC.
P.O. BOX 16446
ARLINGTON, VA 22215

EXAMINER	
LOVE, TREVOR M	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
12/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,951	SHABAT ET AL.	
	Examiner	Art Unit	
	TREVOR M. LOVE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/12/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-175* is/are pending in the application.

4a) Of the above claim(s) *103-160* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-102, 161-175* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made to applicant's response to election/restriction requirement filed 08/12/2008.

Claims 1-175 are pending. Claims 1-102 and 161-175 are currently under consideration. Claims 103-160 are withdrawn as being drawn to non-elect species.

Election/Restrictions

With regards to the Requirement for Restriction/Election filed 06/13/2008, upon careful consideration, the Examiner has determined that Groups I, II, III, and XII should be rejoined since the subject matter associated with the identified groups is not patentably distinct. Rejoinder is therefore deemed proper. Groups I, II, III, and XII are therefore currently under examination.

Furthermore, upon careful consideration, the Examiner has determined that Groups V, VI, and VII should be rejoined since the subject matter associated with the identified groups is no patentably distinct. Rejoinder is therefore deemed proper. Groups V, VI, and VII remain non-elected, and are not currently under consideration.

Upon careful consideration, the Examiner has determined that the species election was improper. The species election has therefore been withdrawn. Claims 1-102 and 161-175 are currently under consideration.

Claim Objections

Claim 83 is objected to because of the following informalities: claim 83 ends with two periods. Appropriate correction is required.

Claim Rejections - 35 USC § 112 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-23, 35-53, 70-77, 84-101, 162-175 are rejected under 35 U.S.C. 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor has possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 10081 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not

necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.*

The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (i.e. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether

applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such a comparison.

I. ***Scope of Claims***

Compounds of Formulas (Ia), (Ib), and (VIIb) as found in claims 16, 22, 46, 52, 70, 76, 94, 100, 172, and 174.

The variables V, B, D, I, F, G, a, b, c, R^1–R^{29} are claimed *broader* than what is supported by the disclosure (see section II below).

Compounds of Formula (III) as found in claims 35 and 162.

The variables n, I, j, k, l, m, p, r, Z, A, Y, X are claimed *broader* than what is supported in the disclosure (see section II below).

II. ***Scope of Disclosure***

Reduction to Practice:

The compounds reduced to practice support the following substituents for the aforementioned variables:

"V" is O;

"B" is C;

"D" is C;

"a", "b", and "c" are 0;

"I", "F", and "G" are not evidenced as having been reduced to practice;

"R^{1}" is CH_2OCON;

"R^{2}" is H;

"R^{3}" is CH_3;

"R^{4}" is H;

"R^{5}" is CH_2OCON;

"R^{6}" is not evidenced as having been reduced to practice;

"R^{7}" is not evidenced as having been reduced to practice;

"R^{8}" is not evidenced as having been reduced to practice;

"R^{9}" is H;

"R^{10}" is H;

"R^{11}" is not evidenced as having been reduced to practice;

"R^{12}" with regards to the structure $-R^{11}C=CR^{12}-$ is not evidenced as having been reduced to practice;

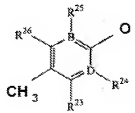
"R^{12}" with regards to *formula IIa* is CH_3;

"R^{13}" is CH_3;

"R^{14}", "R^{15}", "R^{16}", "R^{17}", "R^{18}", "R^{19}" are H;

"R^{20}" is not an identified variable;

"R^{21}" and "R^{22}" are independently



;

"R^{23}" is H;

"R^{24}" is CH_2OCON;

"R^{25}" is CH_2OCON;

"R^{26}" is H;

"R^{27}" is H;

"R^{28}" is H;

"R^{29}" is not evidenced as having been reduced to practice;

It is further noted that the only chemical linker having shown evidence of being reduced to practice is the chemical linker of *formula Ib*, and that the only spacer having shown evidence of being reduced to practice is the chemical linker of *formula IIa*.

"n" is 1;

"i" is 1;

"j" is 1;

"k" is 2;

"l" is 1;

"m" is 0;

"p" is 0;

"r" is 0;

"Z" is 2;

"A" and "Y" are


;

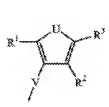
"X" is


.

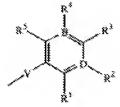
Reduction to Structure or Chemical Formulas

The only disclosure, in addition to the species reduced to practice, is in the form of lists of possible optional substituents for the above mentioned variables. This type of disclosure is not viewed to be a representation of any of the species it encompasses. A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F. 3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (e.g. by reduction to structural/chemical formulae) in addition to those reduced to practice.

The embodiments of the instant invention as exemplified in the drawings do not contain embodiments wherein the variables set forth above are optionally substituted with the following:



Formula Ia



Formula Ib

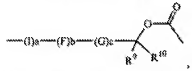
wherein:

V is O, S, PR^6 or NR^7;

U is O, S or NR^8;

B and D are each independently a carbon atom or a nitrogen atom;

R^1, R^2, R^3, R^4 and R^5 are each independently



, hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, hydroxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, amino,

nitro, halo, trihalomethyl, cyano, C-amido, N-amido, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, tetrazole, carboxy, carboxylate, sulfoxy, sulfonate, sulfonyl, suffixy, sulfinate, sulfinyl, phosphonooxy or phosphate, or alternatively, at least two of R^1, R^2, R^3, R^4 and R^5 being connected to one another to form an aromatic or aliphatic cyclic structure;

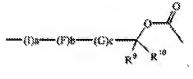
whereas:

a, b and c are each independently as integer of 0 to 5; and

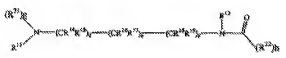
I, F and G are each independently $-R^{11}C=CR^{12}-$ or $-C\equiv C-$, where each of R^{11} and R^{12} is independently hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, hydroxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, amino, nitro, halo, trihalomethyl, cyano, C-amido, N-amido, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, tetrazole, carboxy, carboxylate, sulfoxy, sulfonate, sulfonyl, sulfixy, sulfinate, sulfinyl, phosphonooxy or phosphate, or, alternatively, R^{11} and R^{12} being connected to one another to form an aromatic or aliphatic cyclic structure; and

R^6, R^7 and R^8 are each independently hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, hydroxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, amino, nitro, halo, trihalomethyl, cyano, C-amido, N-amido, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, tetrazole, carboxy, carboxylate, sulfoxy, sulfonate, sulfonyl, sulfixy, sulfinate, sulfinyl, phosphonooxy or phosphate,

provided that at least two of R^1, R^2 and R^3 in Formula Ia and of R^3, R^5, R^7, R^4 and R^5 in Formula Ib are said

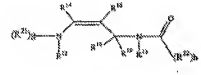


each of R^9 and R^{10} is independently hydrogen or alkyl.



Formula IIa

Formula IIb



Formula IIc

Formula IId

and a combination thereof,

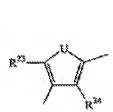
wherein:

d, e, f, g and h are each independently an integer from 0 to 3, provided that d + e + f ≥ 2;

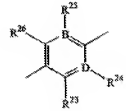
R^{12} and R^{13} are each independently hydrogen, alkyl or cycloalkyl;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are each independently hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, hydroxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, amino, nitro, halo, trihalomethyl, cyano, C-amido, N-amido, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, tetrazole, carboxy, carboxylate, sulfoxy, sulfonate, sulfonyl, sulfixy, sulfinate, sulfinyl, phosphonooxy or phosphate; and

R^{21} and R^{22} each independently has a general formula selected from the group consisting of Formula VIIa and Formula VIIb:



Formula VIIa



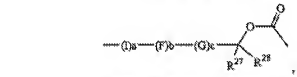
Formula VIIb

wherein:

U is O, S or NR^{28};

B and D are each independently a carbon atom or a nitrogen atom;

R^{23}, R^{24}, R^{25} and R^{26} are each independently



, hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, hydroxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, amino, nitro, halo, trihalomethyl, cyano, C-amido, N-amido, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, tetrazole, carboxy, carboxylate, sulfoxy, sulfonate, sulfonyl, sulfixy, sulfinate, sulfinyl, phosphonooxy or phosphate, or alternatively, two or more of R^{23}, R^{24}, R^{25} and R^{26} being connected to one another to form an aromatic or aliphatic cyclic structure;

whereas:

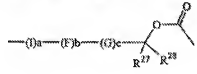
a, b and c are each independently an integer of 0 to 5;

I, F and G are each independently $-R^{30}C{=}CR^{31}-$ or -C≡C-, where each of R^{30} and R^{31} is independently hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, hydroxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, amino, nitro, halo, trihalomethyl, cyano, C-amido, N-amido, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, tetrazole, carboxy, carboxylate, sulfoxy, sulfonate, sulfonyl, sulfixy, sulfinate, sulfinyl, phosphonooxy or phosphate, or, alternatively, R^{30} and R^{31} being connected to one another to form an aromatic or aliphatic cyclic structure; and

R^{29} is hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, hydroxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, amino, nitro, halo,

trihalomethyl, cyano, C-amido, N-amido, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, tetrazole, carboxy, carboxylate, sulfoxy, sulfonate, sulfonyl, sulfixy, sulfinate, sulfinyl, phosphonooxy or phosphate,

provided that two or more of R^{23} and R^{24} in Formula VIIa and of R^{23}, R^{24}, R^{25} and R^{26} in Formula VIIb are



$$Q - Ai - Z^0[(X_0)j(Y_0)k] - Z^1[(X_1)l(Y_1)m] - \cdots - Z^n[(Xn)p(Yn)r] - Z^{n+1}[W]$$

Formula III

wherein:

n is an integer from 0 to 10;

each of i, j, k, l, m, p and r is independently an integer of 0 to 10;

Q is a cleavable trigger unit, as is described hereinabove;

A is a first self-immolative spacer, as is described hereinabove;

Z is an integer of between 2 and 6, representing the ramification number of the dendrimer;

X is a self-immolative chemical linker, as is described hereinabove;

Y is a second self-immolative spacer, as is described hereinabove; and

W is a tail unit,

whereas, when n equals 0, each of l, m, p and r equals 0; and

when n equals 1, each of p and r equals 0.

Preferably, $Z^{n+1}[W]$ comprise two or more functional moieties, being the same or different, and as is described hereinabove.

Further preferably Z equals 2 or 3 and/or n is an integer of 0 to 10.

Correlation between Structure and Function:

A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. Thus, it is not understood what specific structural elements

are essential for the activity of the instantly claimed compounds for the **purposes of drug delivery by way of a self-immolative dendrimer.**

III. ***Analysis of Fulfillment of Written Description Requirement:***

The structural/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC_{50} data of multiple compounds with various types of structural modifications. These types of studies provide insight into the structural limitations that are required for activity, i.e., specific structural elements essential for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

In conclusion, (i) substantial structural variation exists in the genus/subgenera embraced by claims 16-23, 35-53, 70-77, 84-101, 162-175; (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenera claimed; (iii) common structural attributes of the genus/subgenera, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the invention(s), at the time

the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-18, 22-23, 31, 45-48, 52-53, 69-72, 76-77, 83, 93-96, 100-101, and 171-175 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-18, 22-23, 45-48, 52-53, 69-72, 76-77, 93-96, 100-101, and 172-175 recite the limitation "R^9–R^{10}" or "R^{27}–R^{28}" in the description of the structures there within. There is insufficient antecedent basis for this limitation in the claim. The definition of "R^9–R^{10}" is not provided until dependent claims 19, 49, 73, and 97, and the definition of "R^{27}–R^{28}" is not provided. This renders claims 15-18, 22-23, 45-48, 52-53, 69-72, 76-77, 93-96, 100-101, and 172-175 indefinite for failing to clearly set forth the metes and bounds of the instant claims.

Claims 15, 31, 45, 69, 83, 93, and 171 recite "a signal generator agent, a single absorber agent and a combination thereof". It is the position of the examiner, that upon careful consideration the context of the phrase, and evidence from the specification, that applicant intended to write "a signal generator agent, a signal absorber agent and a combination thereof". This appears to be an obvious typo. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-102 and 161-175 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al (U.S. Patent number 6,471,968) in view of De Groot et al (WO 02/083180) (IDS reference) in further view of Greenwald et al (J. Med.

Chem. *Drug Delivery Systems Employing 1,4- or 1,6-Elimination: Poly(ethylene glycol) Prodrugs of Amine-Containing Compounds*).

a. Baker teaches a therapeutic and diagnostic multifunctional system comprising a dendrimer that uses imaging and triggering release of a therapeutic or diagnostic material (see abstract). Said therapeutic agent is taught as being the chemotherapeutic daunorubicin (see column 3, lines 39-55). Baker also teaches that there can also be a diagnostic agent which is a biological monitoring agent such as radioactive labeled elements (see column 4, lines 13-23) this, upon combination with the aforementioned references, reads on **instant claims 15, 31, 34, 41, 45, 69, 83, 93, 171**. Baker also teaches that there can be multiple therapeutic agents attached to the dendrimer that act synergistically (column 16, lines 22-25) this, upon combination with the aforementioned references, reads on **instant claims 9-11, 26-29, 64, 65**. Baker further discloses that the therapeutic agent can be activated upon release, and said release can be enzymatic cleavage or photo-cleavage (see column 4, line 66 through column 5, line 9). Baker also discloses that the composition can comprise a pharmaceutically acceptable carrier (see column 5, lines 19-24). Baker also teaches that the active can be an anti-microbial (see column 3, lines 39-45), this, upon combination with the aforementioned references, reads on **instant claims 33 and 102**.

i. Baker fails to directly disclose that the dendrimer is self-immolative. Baker also fails to disclose the exact structure, for instance, the linker or spacer that is enzymatically cleaved.

b. De Groot teaches a branched composition of the general formula:

$$V\text{-}(W)_k\text{-}(X)_l\text{-}A\text{-}Z$$

-wherein "V" is a specifier, or ***trigger***, which is removed by an enzyme;

-wherein "$(W)_k$-$(X)_l$-A" is a self-eliminating, or ***self-immolative***, spacer system;

-wherein "W" and "X" are each a 1,(4+2n) electronic cascade spacer, or **self-immolative linker**, being the same or different;

-wherein "A" is either:

-a spacer group of formula "$(Y)_m$" wherein "Y" is a 1 ,(4+2n) electronic cascade spacer, or a group of formula OR,

-"U" being a cyclisation elimination spacer, or **self-immolative spacer**;

-wherein "Z" is a therapeutic or diagnostic moiety;

-wherein "k", "l", and "m" are independently an integer from 0 (included) to 5 (included);

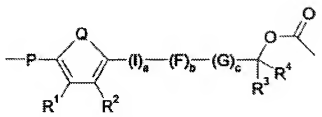
-wherein "n" is an integer of 0 (included) to 10 (included), with the provisos that:

-when "A" is "$(Y)_m$"; "k"+"l"+"m"≥1, and if "k"+"l"+"m"=1, then "n">1 ;

-when "A" is "U": "k"+"l"≥1.

As can be seen by the above composition, De Groot teaches a self-immolative compound comprising a cleavable trigger unit, at least one end unit, self-immolative linkers, and self-immolative spacers, wherein upon cleavage of said trigger unit, the composition self-immolates (see claims 1-4 and abstract), this, upon combination with the above identified references, reads on **instant claims 1, 3, 5, 6, 35, 38, 57, 59, 60, 161, 162**. Said end units comprising anticancer agents such as daunorubicin (see claims 13 and 14), this, upon combination with the above identified references, reads on **instant claims 2, 36, and 163**. Said cleavable trigger unit is disclosed as being enzymatically cleaved (see abstract), this, upon combination with the above identified references, reads on **instant claims 7, 8, 39, 40, 61-63, 82, 87, 88, 165, 166**. Said end units are taught as being either therapeutically effective active agents, or diagnostic agents (see De Groot, page 3, line 6), this, combination with the above identified references, reads on **instant claims 12, 42, 66, 80, 82, 89, 90, 167, and 168**. Components W, X, and A are all taught as being spacers, wherein W and X are taught as being either the same or different (see above description of formula), this, upon combination with the above identified references, reads on **instant claims 4 and 58**. De Groot further teaches that the compound of De Groot can be mixed with a pharmaceutically acceptable carrier for purposes of delivery (see page 16, lines 4-7) this, upon combination with the above identified references, reads on **instant claim 54, 84**.

De Groot further discloses a self-immolative linker with the general formula of:

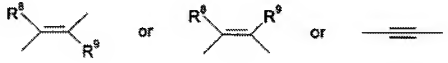


wherein "Q" can be O, S, NR^5, or $-R^5C=CR^6-$, wherein R^5 and R^6 can be hydrogen;

wherein "P" can be NR^7, O, or S;

wherein "a", "b", and "c" are independently an integer of 0 (included) to 5 (included);

wherein "I", "F", and "G" are independently selected from compounds having the formula:

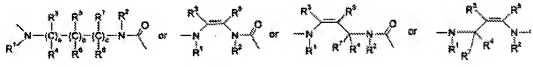


wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 independently represent H, C_{1-6} alkyl, C_{3-20} heterocyclyl, C_{5-20} aryl, C_{1-6} alkoxy, hydroxy (OH), amino (NH_2), mono-substituted amino (NR_xH), di-substituted amino ($NR_x^1 R_x^2$), nitro ($N0_2$), halogen, CF_3, CN, $CONH_2$, $S0_2Me$, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_x$) sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$), and phosphate ($OP(=O)(OR)_2$);

wherein R_x, R_x^1, and R_x^2 are independently selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, two or more of the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, or R^9 optionally being connected to one another to form one or more aliphatic or aromatic cyclic structures.

Said structure, upon combination with the above identified references, reads on **instant claims 16-21, 46-51, 70-75, 94-99, and 172,173.**

De Groot also discloses a self-immolative spacer with the general formula:



wherein "a" is an integer of 0 or 1;

wherein "b" is an integer of 0 or 1;

wherein "c" is an integer of 0 or 1

provided that a + b + c = 2 or 3 ;

wherein R^1 and/or R^2 independently represent H, C_{1-6} alkyl, said alkyl being optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_x), amino (NH_2), mono-substituted amino (NR_XH), di-substituted amino ($NR_x^1R_x^2$), nitro (NO_2), halogen, CF_3, CN, $CONH_2$, SO_2Me, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_x$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$), and

phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1, and R_x^2 are selected fiom a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group;

and wherein R^3, R^4, R^5, R^6, R^7, and R^8 independently represent H, C_{1-6} alkyl, C_{3-20} heterocyclyl, C_{5-20} aryl, C_{1-6} alkoxy, hydroxy (OH), amino (NH_2), mono-substituted amino (NR_xH), di-substituted amino ($NR_x^1R_x^2$), nitro (NO_2), halogen, CF_3, CN, $CONH_2$, SO_2Me, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_20H$), sulphonate ($S(=O)_2OR_x$), sulphonyl ($S(=0)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$), and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1, and R_x^3 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group; and wherein R^1, R^2, R3, R^4, R^5, R^6, R^7, and R^8 can be a part of one or more aliphatic or aromatic cyclic structures, two or more of the substituents R^1, R^2, R3, R^4, R^5, R^6, R^7, and R^8 optionally being connected to one another to form one or more aliphatic or aromatic cyclic structures.

Said structure, upon combination with the above identified references, reads on **instant claims 22, 23, 52, 53, 76, 77, 100, 101, 174, and 175.**

c. Greenwald teaches a tripartite drug comprising a trigger, linker, and drug. Said trigger is enzymatically cleaved. Said drug can be either para-aniline or daunorubicin (see scheme 2 and table 1). Greenwald further discloses that the linker can have the branch that comprises the drug be in different locations (see table 1, specifically, compounds 34b-37b).

d. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Baker, De Groot, and Greenwald. One would have been motivated to do so to allow the composition of Baker to experience release of the therapeutic agents and diagnostic agents upon a single self-immolative triggered event. By modifying Baker with the teachings of De Groot and Greenwald, the composition of Baker would be able to release an increased number of drugs (tail units) upon a single natural or man-made trigger. Furthermore, the single trigger would be able to have a smaller concentration in the self-immolative system than if each cleavage was dependent on individual actions of the trigger. There would be a reasonable expectation in the success of the combination since all three compositions teach enzymatic cleavage of daunorubicin, and all three compositions are designed as therapeutic/diagnostic compositions designed for cancer treatment/diagnosis.

With regards to **instant claims 55 and 56**, it would have been obvious to one of ordinary skill in the art at the time the invention was made to package the pharmaceutical composition and identify its use.

With regards to **instant claims 24-25, 37, 78-79, 85-86, and 164**, it would have been obvious to one of ordinary skill in the art at the time the invention was made to vary the number of generations and ramifications based on the amount of drug desired. Furthermore, in the disclosure of Baker and specifically in Figure 1, Baker teaches increasing the size of a dendrimer by adding

generations, and in Figure 8, Baker teaches increasing the number of ramifications.

Conclusion

No claims are allowed. All claims are rejected. Claim 83 is objected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TREVOR M. LOVE whose telephone number is (571)270-5259. The examiner can normally be reached on Monday-Thursday 7:30-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TL

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
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